

I claim:

1. A method for characterizing the three-dimensional structure of a large molecule comprising the steps of:

5 (a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;

(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;

10 (c) repeating steps (a)-(b) with additional different small molecules; and

(d) utilizing the spectra obtained in steps (a)-(c) to characterize the three-dimensional structure of the large molecule.

15 2. The large molecule characterization method of Claim 1, wherein the three-dimensional structure characterization of step (d) is carried out by feedback modeling according to the following steps:

20 (e) providing data processing means;

(f) providing data storage means;

(g) digitizing raw experimental data acquired according to steps (a)-(c);

(h) storing the digitized data in said data storage means;

25 (i) initializing and running a selected computer program on said data processing means for simulating the experiment

performed in steps (a)-(c);

(j) comparing simulation data obtained from step (i) with the digitized data from the experiment performed in step (g);

(k) if the comparing step (j) produces a result outside a predetermined parameter, establishing a feedback loop and initiating an iterative subroutine whereby the computer simulation adjusts itself, in an incremental way, to fit the simulation to the experimental value, compares the result to the experiment after each computational step and feeds the experimental data back into the input loop of the computation until the result of the comparison of step (j) is within the predetermined parameter.

3. The large molecule characterization method of Claim 1, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

4. The large molecule characterization method of Claim 1, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

5. The large molecule characterization method of Claim 2, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

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6. The large molecule characterization method of Claim 2, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

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7. A method for characterizing the three-dimensional structure of a large molecule comprising the steps of:

(a) mixing a small molecule with a large molecule so that the small molecule binds non-covalently to the large molecule to form a large molecule-small molecule complex;

(b) performing electrospray ionization mass spectrometry to obtain the spectrum of the large molecule-small molecule complex;

(c) using the spectrum from step (b) to calculate the binding constant K_b for the binding of the small molecule complex;

(d) repeating steps (a)-(c) with additional different small molecules;

(e) calculating the heat of formation (ΔH_f) for the binding of each of the small molecules used in steps (a)-(d) to a selected residue on the large molecule;

(f) repeating step (e) for other selected residues on the

large molecule;

(g) comparing the binding constants (K_b) calculated in steps (c) and (d) with the ΔH_f values calculated in steps (e) and (f); and

5 (h) utilizing the comparisons of step (g) to characterize the three-dimensional structure of the large molecule.

8. The large molecule characterization method of Claim 7, wherein said comparing step (g) is carried out by feedback modeling according to the following steps:

10 (i) providing data processing means;
(j) providing data storage means;
(k) digitizing raw experimental data acquired according to steps (a)-(d);
15 (l) storing the digitized data in said data storage means;
(m) initializing and running a selected computer program on said data processing means for simulating the three-dimensional structure of said large molecule according calculations performed in steps (e)-(f);

20 (n) comparing simulation data obtained from step (m) with the digitized data from the experiment performed in step (k);

(o) if the comparing step (n) produces a result outside a predetermined parameter, establishing a feedback loop and initiating an iterative subroutine whereby the computer
25 simulation adjusts itself, in an incremental way, to fit the simulation to the experimental value, compares the result to the

experiment after each computational step and feeds the experimental data back into the input loop of the computation until the result of the comparison of step (n) is within the predetermined parameter.

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9. The large molecule characterization method of Claim 7, wherein the comparisons of step (g) are utilized to identify the residue or residues on the surface of the protein molecule to which the small molecule is bound.

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10. The large molecule characterization method of Claim 7, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

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11. The large molecule characterization method of Claim 7, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

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12. The large molecule characterization method of Claim 8, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

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13. The large molecule characterization method of Claim 8, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

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14. The large molecule characterization method of Claim 9, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

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15. The large molecule characterization method of Claim 9, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.

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16. The large molecule characterization method of Claim 7, further comprising the step of using the heat of formation calculated in step (e) and calculating the heat of reaction (ΔH_{RXN}) for the binding of each of the small molecules used in steps (a)-(d) to a selected residue on the large molecule.

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17. The large molecule characterization method of Claim 16, wherein the large molecule is selected from the group consisting of polypeptides, proteins, DNA, RNA, oligosaccharides, and polymers thereof.

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18. The large molecule characterization method of Claim 16, wherein the small molecules include crown ethers, macrocyclic polyethers, cryptands, and/or polymers of these compounds, or any other suitable ligand or macrocyclic ligand.